UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,958	01/07/2002	Saul Tzipori	21957	5351

7590 02/12/2003

PATREA L. PABST
HOLLAND AND KNIGHT LLP
1201 WEST PEACHTREE ST N.E.
SUITE 2000
ATLANTA, GA 30309-3400

EXAMINER
NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
1645	9

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/041,958	Tzipori et al
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's preliminary amendment filed December 2, 2002 (Paper Number 8) has been received and entered. Claims 1-25 have been canceled and new claims 26-36 have been added. Consequently claims 26-36 are pending in the instant application.

Claim Rejections - 35 USC § 112

1. Claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant's have added new claims which recite dosages of "4 ml serum/at least about 0.5 micrograms/ml/and a dosage of 3 mg human Mab administered to a newborn pig." However, Applicant has not pointed to support within the specification for these new claims. Applicant's are required to demonstrate clear support (i.e., page and line number of specification) or cancel the newly added material.

2. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is vague and indefinite in the recitation of "prevent neurological signs of HUS..." One of skill in the art would be unable to determine the metes and bounds of the claimed invention. What criterium is being used to evaluate a neurological sign? Is a specific tract being inhibited, and if so to what degree? Is the sign one that is clinically manifest or simply detectable by analyzing body fluids? Without a clear definition as to the specific "neurological sign" as well as the degree to which they are affected, one of skill in the art would be unable to determine the metes and bounds of the phrase "prevent neurological signs."

3. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is vague and indefinite in the recitation of "at least about 0.5 micrograms/ml." One of skill in the art would be unable to determine the metes and bounds of the claimed invention. "At least" one thousand degrees in claim means minimum temperature of one thousand degrees "About" in claim allows some tolerance. National Research Development Corp v. Great

Lakes Carbon Corp. (DC Del) 188 USPQ 327. Consequently, the term at least about confers two separate contradictory limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 26-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krivan et al and Perera et al in view of Queen et al and Engelman et al.

The claims are drawn to a dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II, to prevent or treat hemolytic uremic syndrome in a human.

Krivan et al (U.S. Patent Number 5,512,282) disclose of purified high titer, monospecific polyclonal antibodies to Shiga-like toxin obtained by a process of inoculating a bovine animal with a purified active SLT derived from *E. coli* and selected from the group consisting of SLT I, SLT II, SLT IIV and mixtures thereof. Krivan et al further disclose of the passive immunization of a human or animal against SLT toxinemia comprising administering to the human or animal a prophylactically effective amount of the elicited antibody. (See claims 1 and 17). Krivan et al further disclose that SLT toxinemia can lead to hemolytic uremic syndrome. (See column 1). Krivan et al further disclose that "the present invention provides an antitoxin to **one** or more SLTs." (See column 6). Krivan et al further disclose that "A **single type of SLT, such as SLT-II** or a variant thereof, such as SLT-IIvp, can be injected. This provides polyclonal antibodies that are monospecific to just that type of SLT or variant." (See column 8).

Perera et al (Journal of Clinical Microbiology Vol 26, No. 10, pp 2127-2131, October 1988) teach of five monoclonal antibodies which bind to the α-subunit of SLT-II and were able to neutralize the toxin. (See abstract).

Neither Krivan et al nor Perera et al teach of monoclonal human or humanized antibodies.

Queen *et al* (WO90/07861) teach that methodology for the production of CDR-grafted antibodies having CDRs derived from the variable regions of non-human antibodies and framework regions derived from human antibodies were well established in the art at the time the claimed invention was made and that CDR-grafted antibodies were recognized to be useful reagents for diagnostic and therapeutic applications. Queen et al further set forth that humanized antibodies are substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin. (See abstract).

Engelman *et al* (Human Hybridomas and Monoclonal Antibodies. New York Plenum Press. 1985 pp 23-27) teach that methods for constructing human-human hybrids that secrete human monoclonal antibodies using lymphoblastoid cell lines as fusion partners were well known in the art at the time of applicants invention.

Given that 1) Krivan et al have disclosed of methods of passive immunization comprising administering high titer, monospecific polyclonal antibodies against Shiga-like toxin II, and that 2) Perera et al have demonstrated neutralization of SLT-II with monoclonal antibodies which specifically bind the α-subunit of SLT-II, and that 3) Queen et al has taught of the advantages of humanized antibodies over non-human antibodies for therapy in humans, and that 4) Engelman et al has also taught of the advantages of human monoclonal antibodies over non-human monoclonal antibodies for therapy in humans, it would have been prima facie obvious to one of ordinary skill in the art to have generated a humanized antibody or a human monoclonal antibody as taught by

Queen et al and Engelman et al, for use in the method disclosed by Krivan et al. One would have been motivated to produce such an antibody based on the advantages described by Queen et al and Engelman et al, (i.e., substantially decreased immunogenicity). One would have been further motivated to humanize an antibody which binds the α-subunit of SLT, based on the demonstration of neutralization as shown by Perera et al.

It is noted that the references do not teach the amount of antibodies set forth in claims 34 or 36. However, determining the precise dosage of a humanized antibody is merely the result of optimizing a result effective variable. As set forth In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219, (CCPA 1980), it is normally within the skill in the art to optimize a result effective variable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

February 7, 2003